## REMARKS

### *Status of the Claims*

Claims 1-19 and 22-24 are in the application.

Claims 1-19 and 22-24 are rejected.

By way of this amendment, claims 1, 4, 7, 10, 13, 14, 15 and 17 have been amended, claims 3, 9 and 16 have been canceled, and new claims 25 and 26 have been added.

Upon entry of this amendment, claims 1, 2, 4-8, 10-15, 17-19 and 22-26 will be pending.

### *Summary of the Amendment*

Claim 1 has been amended to incorporate the limitations of claim 3. In addition, claim 1 has been amended to more clearly reflect that the nucleic acid sequence encoding the immunogen is on a different nucleic acid molecule from the nucleic acid sequence encoding the immunomodulating protein. Support for the amendment is found in the claims as filed and throughout the specification such as on pages 17, 25 and 26.

Claim 3 has been canceled in view of the amendment to claim 1.

Claim 4 has been amended to correct dependency in view of the amendment to claim 1 and cancelation of claim 3.

Claim 7 has been amended to incorporate the limitations of claim 9. In addition, claim 7 has been amended to more clearly reflect that the nucleic acid sequence encoding the immunogen is a separate expressible sequence from the nucleic acid sequence encoding the immunomodulating protein. Support for the amendment is found in the claims as filed and throughout the specification such as on pages 17, 25 and 26.

Claim 9 has been canceled in view of the amendment to claim 7.

Claim 10 has been amended to correct dependency in view of the amendment to claim 7 and cancelation of claim 9.

Claims 13 and 14 have been amended to correct an obvious typographical error.

Claim 15 has been amended to incorporate the limitations of claim 16. In addition, claim 15 has been amended to more clearly reflect that the nucleic acid sequence encoding the immunogen is a separate expressible sequence from the nucleic acid sequence encoding the immunomodulating protein. Support for the amendment is found in the claims as filed and throughout the specification such as on pages 17, 25 and 26.

Claim 16 has been canceled in view of the amendment to claim 15.

Claim 17 has been amended to correct dependency in view of the amendment to claim 15 and cancelation of claim 16.

New claims 25 and 26 correspond to claims 13 and 14 but are dependent upon claim 7 instead of claim 1. Support for the amendment is found in the claims as filed.

No new matter has been added.

***Claim Rejections – 35 USC § 102***

**Taylor**

Claims 1, 2, 7, 15 and 22-24 have been rejected as being anticipated by Taylor et al. (J. Leukocyte Biology Sept. 2002, Vol. 72, pp. 522-529).

Taylor discloses fusion proteins, and nucleic acid constructs encoding them, which comprise OX40 extracellular domain linked to the Fc domain of human IgG. The fusion proteins in Taylor are intended to inhibit immune reactions. Taylor teaches the inclusion of the OX40 portion of the fusion protein to deliver the fusion protein to cells targeted for destruction. The presence of the IgG sequences are provided to facilitate elimination of the immune cells to which the OX40 binds by processes involving the IgG portion. Taylor further reports that the OX40 portion functions to inhibit immune responses associated with colitis in mice.

The claims are not anticipated by Taylor. The claimed invention is not a fusion protein. In addition, the claims have been amended to recite that the immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases. Claim 1 refer to the nucleic acid coding sequence encoding the immunomodulatory protein being on a separate nucleic acid molecule as the nucleic acid coding sequence encoding the

immunogen. Claim 7 and 15 refer to the nucleic acid coding sequence encoding the immunomodulatory protein as being linked to regulatory sequences separately from the nucleic acid coding sequence encoding the immunogen. Taylor does not describe compositions in which coding sequences for the immunogen are separate from coding sequences for the immunomodulating protein, whether on separate molecules or the same molecule. Taylor teaches using OX40 to deliver IgG sequences in order to kill cells by complement lysis and ADCC as well as the immune suppressive activity of OX40. The fusion proteins set forth in Taylor do not contain every element of the claimed invention and therefore, Taylor does not anticipate the claimed invention.

Applicants respectfully request that the rejection of claims 1, 2, 7, 15 and 22-24 as being anticipated by Taylor et al be withdrawn.

**Zhan**

Claims 1, 2, 7, 8, 13, 15 and 22-24 have been rejected as being anticipated by Zhan et al. (DNA AND CELL BIOLOGY, 2000, Vol. 19, No. 11, pp637-645).

Zhan describes a plasmid containing a transgene comprising coding sequences for a fusion protein which includes sequences of a soluble form of OX40 and the CH2 and CH3 domains of Mouse IgG2a. The transgene was under the control of the CMV promoter. Transgenic mice produced with the transgene were observed to express the fusion protein in pancreatic tissue.

The claims are not anticipated by Zhan. The claimed invention is not a fusion protein. In addition, the claims have been amended to recite that the immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases. Claim 1 refer to the nucleic acid coding sequence encoding the immunomodulatory protein being on a separate nucleic acid molecule as the nucleic acid coding sequence encoding the immunogen. Claim 7 and 15 refer to the nucleic acid coding sequence encoding the immunomodulatory protein as being linked to regulatory sequences separately from the nucleic acid coding sequence encoding the immunogen. Zhan does not describe compositions in which coding sequences for the immunogen are separate from coding sequences for the

immunomodulating protein, whether on separate molecules or the same molecule. Zhan teaches using a fusion protein encoded by a transgene as a marker for identifying sites of expression in a transgenic animal. The fusion proteins set forth in Zhan do not contain every element of the claimed invention and therefore, Zhan does not anticipate the claimed invention.

Applicants respectfully request that the rejection of claims 1, 2, 7, 8, 13, 15 and 22-24 as being anticipated by Zhan et al be withdrawn.

**O'Hare**

Claims 1-5, 7-11, 13-17 and 22-24 have been rejected as being anticipated by U.S. Patent No. 6,017,735 to O'Hare et al.

O'Hare discloses coupled proteins such as fusion proteins, and nucleic acid constructs encoding them, including a coupled protein that comprises HSV VP22 protein and an immunomodulating protein such as OX40. According to O'Hare, the VP22 portion of the coupled protein has intercellular trafficking functions and facilitates distribution/delivery of the immunomodulating protein coupled to it. The proteins in O'Hare are necessarily coupled since the VP22 protein sequences are provided in order to help direct the immunomodulating proteins.

The claims are not anticipated by O'Hare. The claimed invention is not a fusion protein. Claim 1 refer to the nucleic acid coding sequence encoding the immunomodulatory protein being on a separate nucleic acid molecule as the nucleic acid coding sequence encoding the immunogen. Claim 7 and 15 refer to the nucleic acid coding sequence encoding the immunomodulatory protein as being linked to regulatory sequences separately from the nucleic acid coding sequence encoding the immunogen. O'Hare does not describe compositions in which coding sequences for the immunogen are separate from coding sequences for the immunomodulating protein, whether on separate molecules or the same molecule. O'Hare teaches delivering OX40 by linking it to VP22. The combination of the two is necessarily physically linked. The fusion proteins set forth in O'Hare do not contain every element of the claimed invention and therefore, O'Hare does not anticipate the claimed invention.

Applicants respectfully request that the rejection of claims 1-5, 7-11, 13-17 and 22-24 as being anticipated by O'Hare et al be withdrawn.

**Emtage**

Claims 1-4, 7-10, 13-19 and 22-24 have been rejected as being anticipated by Emtage et al in U.S. Published Application No. US2003/0113919.

Applicants respectfully urge that the Office has incorrectly characterized the teachings in Emtage. Specifically, although the punctuation obscures its clarity, Emtage discloses using OX40 Ligand, not OX40. Emtage discloses targeting cells that express OX40, which is the alternative name for OX40 Receptor using the OX40 Ligand.

Paragraph [0066] of the published application states

> In certain embodiments, it may be advantageous to combine a nucleic acid sequence encoding an immunogenic target with one or more co-stimulatory component(s) such as cell surface proteins, cytokines or chemokines in a composition of the present invention. The co-stimulatory component may be included in the composition as a polypeptide or as a nucleic acid encoding the polypeptide, for example.

Emtage goes on to state in paragraph 66 that

> Suitable co-stimulatory molecules include, for instance,
>
> • polypeptides that bind members of the CD28 family such as the CD28 binding polypeptides B7.1 and B7.2;
>
> •polypeptides which bind members of the integrin family including members of the ICAM family (i.e., ICAM-1, -2 or -3);
>
> •polypeptides which bind CD2 family members (i.e., CD2, signalling lymphocyte activation molecule such as CD58 or SLAM ligands;
>
> •polypeptides which bind heat stable antigen;
>
> •polypeptides which bind to members of the TNF receptor (TNFR) family (i.e., 4-1BB (CD137), OX40 (CD134;), and CD27) such as 4-1BBL (4-1BB ligand; TNFR associated factor-1 (TRAF-1; 4-1BB ligand;), TRAF-2 (4-1BB and OX40 ligand;),

TRAF-3 (4-1BB and OX40 ligand), OX40L (OX40 ligand;), TRAF-5 (OX40 ligand), and CD70 (CD27 ligand).
•CD154 (CD40 ligand or "CD40L"; may also be suitable.

(paragraph 66, bullet points added). Of this list of co-stimulatory molecules, the "polypeptides which bind to members of the TNF receptor (TNFR) family" section is confusing but, when properly read, does not state what the Office asserts it state. The recitation of "OX40 (CD134)" in this section is provided as one of a list of three(3) proteins "which are members of the TNF receptor (TNFR) family". When Emtage states that "polypeptides which bind to members of the TNF receptor (TNFR) family", it is saying "polypeptides which bind to 4-1BB (CD137), OX40 (CD134;), and CD27". That is, OX40, along with 4-1BB and CD27 are the targets of the co-stimulatory molecules provided. This is clear in that the paragraph states "such as" and provides a list of molecules that bind to 4-1BB, OX40 or CD27. A careful review of paragraph [66] reveals that Emtage teaches using OX40L, not OPX40.

Thus, the claims are not anticipated by emtage. The claimed invention refers to OX40, not OX40L. Emtage does not describe compositions which include coding sequences for the immunogen and coding sequences for the OX40 protein. Emtage teaches delivering OX40 Ligand to target cells that express OX40. Emtage does not contain every element of the claimed invention and therefore, does not anticipate the claimed invention.

Applicants respectfully request that the rejection of claims 1-4, 7-10, 13-19 and 22-24 as being anticipated by Emtage et al be withdrawn.

***Claim Rejections – 35 USC § 103***

**Emtage and Clement**

Claims 1-19 and 22-24 have been rejected under 35 U.S.C. 103 as being unpatentable over Emtage et al in U.S. Published Application No. US2003/0113919 in view of Clement et al. J. Infect. dis. 2002, 185, pp. 165-173.

As noted above, Emtage teaches using OX40L, not OX40 as an immunomodulating protein. Clement is asserted to disclose vaccines using HSV gD. Nothing in Clement makes up for this deficiency in Emtage. The combination of Emtage and Clement do not yield the present invention. The references, when combined, do not disclose every element of the claimed invention. Nothing in the combination of references teaches or suggests the claimed invention. The claims are not *prima facie* obvious in view of the combination of Emtage and Clement.

Applicants respectfully request that the rejection of claims 1-19 and 22-24 under 35 U.S.C. 103 as being unpatentable over Emtage in view of Clement be withdrawn.

**O'Hare and Clement**

Claims 1-19 and 22-24 have been rejected under 35 U.S.C. 103 as being unpatentable over O'Hare et al in U.S. Patent No. 6,017,735 in view of Clement et al. J. Infect. dis. 2002, 185, pp. 165-173.

O'Hare and Clement are discussed above. O'Hare discloses coupled proteins such as fusion proteins, and nucleic acid constructs encoding them, including a coupled protein that comprises HSV VP22 protein and an immunomodulating protein such as OX40. The VP22 protein in O'Hare is provided to facilitate delivery of the second protein. The VP22 protein is provided to perform a specific function. Nothing suggest that the gD protein disclosed in Clement performs the same or similar function. One skilled in the art, following the teachings of O'Hare, would not substitute the VP22 protein with gD protein. O'Hare teaches that the presence of VP22 is essential in the coupled protein. O'Hare teaches away from replacing VP22 with a different protein.

Moreover, O'Hare teaches away from the claimed invention in that the proteins in O'Hare are necessarily coupled so that the VP22 portion can facilitate intercellular delivery of the second protein, such as OX40. O'Hare discloses that when VP22 is expressed in a cell, it spreads to adjacent cells by a mechanism not well understood. Thus, its purpose in the coupled proteins taught in O'Hare is to facilitate the spread of the second protein, such as OX40, which is physically attached to it. O'Hare not only teaches away from using a different viral protein but additionally teaches away from separate proteins. The proteins in O'Hare are necessarily linked

and one skilled in the art would not, following the teachings in O'Hare, create plasmids and compositions in which the OX40 and immunogen are separate. The claims are not *prima facie* obvious in view of the combination of O'Hare and Clement.

Applicants respectfully request that the rejection of claims 1-19 and 22-24 under 35 U.S.C. 103 as being unpatentable over O'Hare in view of Clement be withdrawn.

***Conclusion***

Claims 1 – 19 and 22-24 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully Submitted,

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